RESEARCH COMMUNICATION

Linking Histopathology and Family History in Breast Cancer

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Abstract

In order to assess the prognostic value of family history (FH) of malignancies in patients afflicted with breast cancer (BC), we examined FH and histopathologic characteristics of 542 Iranian primary BC patients. Cases with distant metastasis at the time of diagnosis were excluded. Mean age of the studied population was 49 and the most common presenting stage was stage IIA followed by stage IIB.

Data on a total of 6089 relatives (1st to 4th generations with the assumption of probands as the 3rd generation) were gathered. FH of BC and other malignancies (OM) was positive in 29 and 54% of cases, respectively. The most common OM's were gastric (67), lung (52) and uterus (47) cancers.

We found that a FH of BC does not have any significant correlation with proven prognostic factors but a history of BC among relatives at or before the age of 36 is associated with more aggressive tumours. On the other hand, although FH of OM was associated with an older age of the probands (which is generally associated with a favourable prognosis), tumours of the cases with FH of OM had higher grades, lymphatic invasion being detected more frequently. Also we noted that the younger the age of the relatives diagnosed with cancer, the higher the stage of the probands themselves.

All together our study indicates the possibility of a relation between FH of BC and OM, and histopathologic characteristics of the probands' tumours which would put forward FH as a prognostic factor rather than a simple risk factor in BC.

Key Words: Breast cancer - histopathology - family history - prognostic factors - other malignancies - risk factors

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Abbreviations: Family History (FH), Breast Cancer (BC), Malignancies other than Breast Cancer (OM).

Background

The high frequency of breast cancer (BC) and its role as the second leading lethal cancer (after lung cancer) (Andreoli et al., 2001) has provoked much attention to develop strategies for risk assessment (and identifying high risk populations), early detection, predicting the individual outcome and determining the usage of more aggressive treatments.

In order to achieve these goals, identifying the risk factors (which influence one's risk of developing breast cancer) and the prognostic factors (which influence the patient's outcome and the severity of the disease) are two essential components. Markers of prognosis perdict patient outcome irrespective of the treatment given (McGuire and Clark, 1992; Gasparini, 1998; Hayes et al., 1998). In general, such factors reflect biologic characteristics of the tumours including proliferation, invasion, and mobility (Isaacs et al., 2001).

Using prognostic factors, patients with early stage breast cancer might be assigned to one of several deifferent

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outcome categories (Hayes et al., 1998), which in turn may guide systemic treatment recommendations. These prognostic factors are classified into three different categories based upon the predictive strength of the factor (Table 1).

The most important risk factors of BC include older age, positive family history (FH), early menarche, late menopause, first term pregnancy after age 25 years, null parity, exposure to radiation (as in radiotherapy), and perhaps use of exogenous estrogen (Andreoli et al., 2001). Moreover, epidemiological studies have suggested some dietary factors (such as high fat intake) as other risk factors, but the causative links remain to be revealed (Andreoli et al., 2001).

Of all these factors, the FH is perhaps the oldest and the most attractive issue. A positive FH of BC is defined as having one or more blood relatives who have, or have had BC. These relatives could be on either the father or mother's side of the family. Relatives by marriage (in-laws) or by adoption do not count in determining the family risk of disease. (Breast Cancer and Family History, 1997) Talking about the importance of FH of BC in increasing the risk, it is essential to know:

- The number of relatives with breast cancer
- How many close relatives (first degree relatives) have or have had breast cancer
- The age that the breast cancer was diagnosed (Breast Cancer and Family History, 1997).

Identification of BC susceptibility genes, BRCA1 and BRCA2, raised hope to reveal the underlying mechanisms of BC inheritance but further studies showed that only 5 to 10% of BC cases are associated with these genes, while the mutations themselves do not seem to have full penetrance in carriers; Altogether it is indicating that other not yet fully identified genetic and evironmental factors should be responsible (Andreoli et al., 2001).

In cross-sectional studies of adult populations, 5% to 10% of women have a mother or sister with breast cancer, and about twice as many have either a first-degree or a second-degree relative with breast cancer. (Yang et al., 1998; Colditz et al., 1993; Slattery and Kerber, 1993; Johnson et al., 1995) The risk conferred by a family history of breast cancer has been assessed in both case-control and cohort studies, using volunteer and population-based samples, with generally consistent results (Pharoah et al.,1997). In a pooled analysis of 38 studies, the relative risk of breast cancer conferred by a first-degree relative with breast cancer was 2.1 (95% confidence interval (CI) 2.0-2.2) (Pharoah et al.,1997). Risk varies with the age at which the affected relative was diagnosed: the younger the age of the affected relative, the greater the risk posed to relatives (Yang et al., 1998; Colditz et al., 1993; Slattery and Kerber, 1993; Pharoah et al.,1997; Negri et al., 1997; Hemminki et al., 1998). This effect was strongest for women under 50 who had a first-degree relative affected before age 50 (Pharoah et al.,1997).

Table 1. Proven Breast Cancer Prognostic Factors.

Strength	Relative Risk of recurence	Prognostic Marker
Strong	>2	TNM stage
	>2	Axillary nodal status
	>2	Tuomor size
Moderate	1.5-2	Tuomor grade
	1.5-2	Lymphatic or vascular invasion
Weak	2>	ER content
	2>	PR content

The number of affected relatives and the closeness of their biologic relationship are also important factors (Colditz et al., 1993; Slattery and Kerber, 1993; Pharoah et al.,1997). In general, the greater the number of affected relatives and the closer the biologic relationship, the greater the risk (Colditz et al., 1993; Slattery and Kerber, 1993; Pharoah et al.,1997). The number of female relatives in the family influences both utility and significance of the family history. In families with few women, it may be difficult to identify a genetic susceptibility to cancer, even if a genetic susceptibility is present. If a family has many female family members, the proportion of affected to unaffected may be a more important indicator of risk than the absolute number of affected relatives.

Moreover, a few investigators have focused on the possible link between having an FH of BC and the prognosis of the disease, which would put forward FH as a prognostic factor rather than a sole risk factor. In a study of 733 young BC patients (Malone et al., 1996) researchers found that women who had a first-degree family history of BC experienced increased survival and this finding was not attributable to differences in screening or treatment. More recently, an other study (Mohammed et al., 1998) compared the clinicopathological characteristics of breast tumours between 95 FH (+) and 329 FH (-) women with BC and found that there was a trend for the FH (+) patients to have slightly smaller tumours (mean size 2.49 vs. 3.04 cm, $p=0.09$) and also a significantly greater proportion of the familial cases had grade III infiltrating ductal carcinoma (40% vs. 27%, $p=0.02$). Despite this, there were more cases of operable node-negative disease among the study group than among the controls (48% vs. 32%, $p=0.004$) and there was a highly significant survival advantage for patients with a positive FH ($p<0.001$).

More distinct histopathologic differences are noted, when the BRCA1 and 2 mutations are considered (Couch et al., 1997; Shattuck-Eidens et al., 1997) : Both BRCA1 and 2 mutation carrier tumours are of higher grade than are sporadic cases. An excess of medullary/atypical medullary carcinoma has been reported in patients with BRCA1 mutations. Multifactorial analysis, however, shows that the only features independently associated with BRCA1 mutations are a high mitotic count, pushing tumour margins and a lymphocytic infiltrate. For BRCA2 mutation, an association with tubular/lobular carcinoma has been suggested, but not substantiated in a larger Breast Cancer Linkage Consortium study. In multifactorial analysis, the independent features were a lack of tubule formation and pushing tumour margins only (Lakhani, 1999).

Conversely, other study of 201 young early-stage BC patients (Chabner et al., 1998) found that the rates of local, regional and distant recurrence and disease-free or overall survival did not differ between FH (+) and FH (-) patients and these findings were confirmed in an other study too. (Harrold et al., 1998) Moreover, in a review of 583 BC patients (Tsuchiya et al., 1998) researchers didn't find any differences for any of mean age, menopausal status, histological staging, and estrogen receptor status between FH (+) and FH (-) patients.

Finally, considering the rather limited role of BRCA1/2 genes mutations in familial BC's, an other group (Lakhani et al., 2000) analyzed 82 BC patients from non-BRCA1/2 families and found out that BC's in these families were of significantly lower grade (p=0.001), showed less nuclear pleomorphism (p=0.0002), and had a lower mitotic count (p=0.003) in comparison with control BC unselected for a FH of the disease.

But what is the role of the family history of other cancers in this context? So far, the main focus has been on the importance of FH of malignancies other than BC (OM) as risk factors (including a previous article by the author (Atri et al., 2001)) and the leading and most significant association has been found between the FH of ovarian cancer and increasing risk of BC.

A first-degree relative with ovarian cancer confers a modest risk of BC, e.g., the odds ratio derived from a case-control study based on the Utah Cancer Registry was 1.27 (95% CI 0.91-1.77), (Kerber and Slattery, 1995) and other studies have found no evidence of increased risk (Negri et al., 1997; Auranen et al., 1996). When the Utah data were analyzed according to a FH score (based on characteristics that included number of relatives with ovarian cancer, their age of diagnosis, and biologic relatedness), however, the odds ratio for women with a score of 5 or greater (3% of the population) was 1.60 (95% CI 1.03-2.43), and for women with scores of 2.0 to 4.9 (12% of the population), the odds ratio was 1.15 (95% CI 1.01-1.36).[Kerber and Slattery, 1995] The presence of both breast and ovarian cancer in a family increases the likelihood that a cancer-predisposing mutation is present (Lakhani et al., 2000; Yang et al., 1998).

The other candidate cancers, associated with an increased risk of BC occurance are uterus, colon and prostate cancers. Yet, there exist much debate for (Andreoli et al., 2001; Familial breast cancer risks, 1993; Andrieu et al., 1994; Slattery and Kerber, 1994) or against (Familial breast cancer risks, 1993; Andrieu et al., 1991; Lin et al., 1999) these associations.

Our review of the literature and existing articles failed to provide us with any notable reports regarding the possible relation between FH of OM and the characteristics of the patients tumours and their prognosis.

The last but not least thing to consider is the extend to which the pedigrees and family hisrory-based data are reliable. Most investigators attempt to confirm cancer histories in relatives from medical records, cancer registries, or death certificates. However, this is becoming increasingly difficult with greater emphasis on confidentiality and early destruction of hospital records (Evans et al., 1996). However, mere relying on interviews with patients and their relatives would subject the findings to some degrees of bias and uncertainty.

Patients and Methods

In order to evaluate the relation between FH of breast cancer (BC) and other malignancies (OM), and the histopathologic characteristics of BC patients and the known prognostic factors, we performed a retrospective study on a database of 542 Iranian patients, diagnosed with primary BC. Reqruitment was carried out from 1993 to 1999.

The patients were mostly middle to high class citizens of Tehran, who were examined and followed up by a surgeon in a private-practice outpatient clinic. The patients were put through comprehensive clinical and paraclinical investigation and suspected cases underwent biopsy and/or total masectomy, if necessary. All of the cases received adequate treatment according to the latest protocols.

Staging was performed using physical examination and paraclinic findings (including radiologic studies and routine blood tests), and patients with distant metastasis at the time of diagnosis (stage IV) were excluded from the study.

Tumour slides were reviewed by a set of selected expert pathologists and Estrogene and Progestrone receptors (ER and PR, respectively) were analysed immunohistochemicaly on samples from parafine embeded blocks of the tumours.

Patients and their relatives were interviewed by a geneticist and detailed pedigrees were drawn for all the patients. Each interview took an average of an hour. The pedigrees include all healthy and diseased, (wheater cancer afflicted or not) and alive or dead family members from the grand-parents to the patrients' offspring genaration including 1st to 4th degree relatives of the probands. Family trees were often drawn on the basis of patients and their relatives claims and whenever possible, firm evidence (e.g. reports) was used to increase the accuracy and reliability of the gathered data.

Altogether, detailed histopathologic and pedigree data were used to construct the database which was subsequently analysed using SPSS program (SPSS for Windows, Release 10.0.1, Standard Version, Copyright " SPSS Inc., 1989-1999). Depending on the type of the variables, suitable statistical analysis (e.g. chi-square, t—test, ANOVA, and regression-correlation) was applied.

Results

The patients included 536 women and 6 men with the mean age of 49 (std dev 11.22; range 15-82). Of these, 67 (12.5%) cases were diagnoses at the age of 36 or younger. The tumours were mostly unilateral (502 vs. 16) with ductal pathology (ductal 471[87.9%]; lobular 41[7.6%]; mixed ductal and lobular 7[1.3]).

The tumours were mostly high grade (63.8%). Mean tumour size was 3.28cm (std dev 4.2652; range microscopic

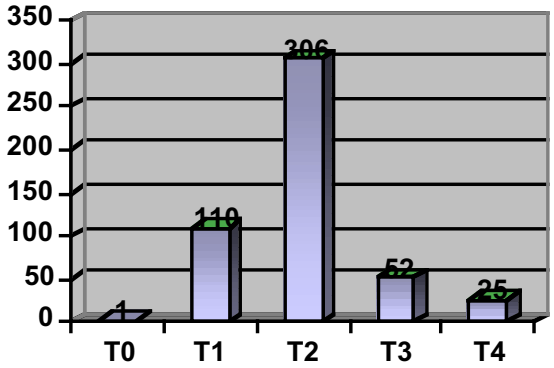

Figure 1. Tumour Size Distribution in Studied Population. (T0 = no evidence of the primary tumour; T1 = tumour<2 cm, T2 = 2<tumour<5 cm, T3 = tumour>5 and T4 = skin or chest wall involvement)

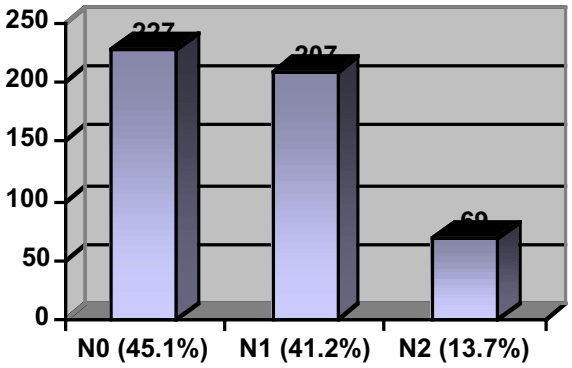

Figure 2. Axillary Nodal Involvement. (N0 = no regional lymph node involvement, N1 = metastasis to movable ipsilateral nodes, N2 = metastasis to ipsilateral nodes fixed to one another or to other structures)

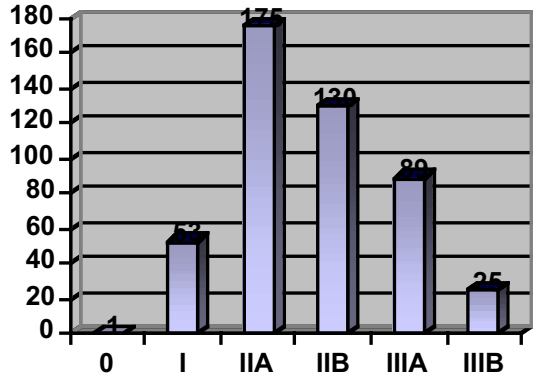

Figure 3. TNM Staging of the Tumours.

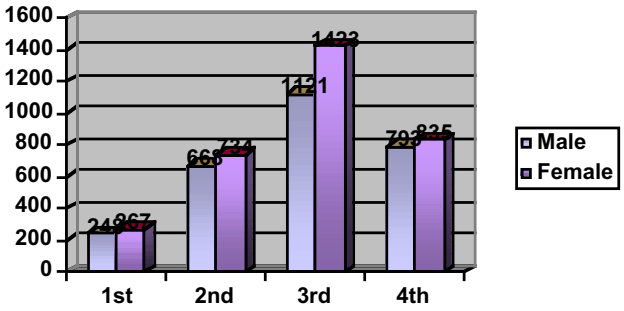

Figure 4. Total Number of Relatives in Pedigrees According to Sex and Generation (Patients Excluded).

to 25cm) (Fig 1). Axillary lymph node (ALN) involvement was detected in 54.4% of the cases and perinodal invasion was found in 25.9% of these cases (Fig 2). Stage was calculated using conventional TNM criteria of American Joint Committee on Cancer classification for breast cancer (Doherty et al., 1997), with assumption of M=0 as explained above (Fig 3).

Vascular and lymphatic invasion was found in 50% and 17% of the tumours, and 61% and 62.5% of the tumours showed positive ER and PR staining respectively.

Data on a total of 6089 relatives (1st to 4th generation, assuming 3rd generation as the probands' generation) were gathered (Fig 4). Rate of Consanguinity among patients and their parents were 16 and 15.8% respectively.

A positive FH of BC was noted in 29% of cases' pedigrees; A total of 219 BCs (excluding probands) were found in these pedigrees (70 1st, 69 2nd, 75 3rd , and 5 4th degree relatives afflicted). Of these, 31 pedigrees had at least one BC case, diagnosed at the age of 36 or younger (9 first-degree and 6 second-degree relatives of the probands).

Fifty-four percents of the patients had a positive FH of OM with a total of 469 cases afflicted (179 1st, 162 2nd, 143 3rd, and 12 4th degree relatives). The most common cancers in these pedigrees included gastric (67), lung (52), uterus (47), heamatopoietic (acute and chronic leukaemia) (41), brain (34), colorectal (30), esophagous (28) and prostate (28), liver (25), lymphoid tissue(lymphoma) (24), thyroid (15) and ovary (7) cancers.

Discussion

FH of BC was not associated with FH of OM (chi-square=0.742, df=1) but considering the number of cases, it was noted that with the number of BC cases increased, the number of OM cases also increased in the pedigrees ($p<0.001$).

Whilst age of the patients was independent of the FH of BC, it was related to the FH of OM; Mean age of the patients with FH of OM in their 1st degree relatives was significantly higher than those without it (51.72 vs. 47.99 yrs., t=3.436, df=535, sig.(2-tailed)=0.001, 95% CI of difference=1.5965-5.85.92) (Table 2). The same effect was also noted considering the total number of 1st degree cancer (including BC) cases in pedigrees: 51.27 vs. 47.79 yrs. (t=3.442, df=535, sig.=0.001).

Also, mean age of the patients with a positive FH of prostate cancers and leukaemia was higher: For FH of prostate cancer (28 cases) 54.65 vs. 48.69 (t=2.655, df=535, sig.=0.008), and for leukaemia (41 cases) 52.33 vs. 48.72 (t=2.311, df=535, sig.=0.025). Same effect was noted among

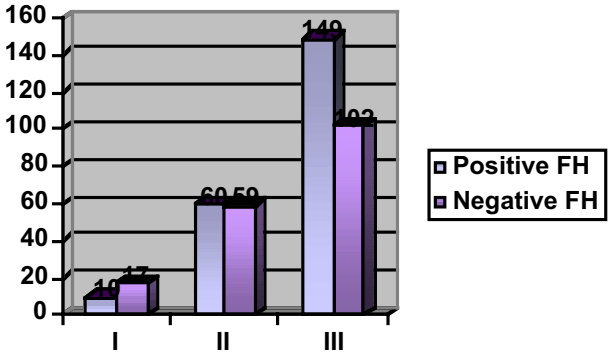

Figure 5. Patients' Tumour Grade and FH of Cancers other than BC.

cases with an FH of uterus cancers in their 1st degree relatives(n=15)(54.93 vs. 48.81, t=2.08, df=535, sig.=0.037).

Most of the bilateral cases had FH of BC (chi-square=5.45, df=1, sig.=0.019) (Table 3). Cases with FH of OM had higher grade tumours (p=0.012) (Fig. 5). Considering the number of cancers in each pedigree and degree of relatives, the most significant correlation was noted between the patients' tumour grade and the number of cancers in their 2nd degree relatives (p=0.026).

Patients with FH of prostate cancer (n=28) had lower TNM stage, but the correlation was not highly significant (p=0.053). On the other hand, stages of the patients who had an FH of esophagous cancer (n=28) were significantly (p=0.033) lower. Finally, younger mean age of the cancer-afflicted relatives was associated with higher patients' stages (p=0.002) (Table 4), and more involvement of ALN (Mean age of 51.61 and 57 yrs in patients with and without ALN involvement respectively, t=-2.645, df=240, sig.=0.009).

Table 2. Mean Age of the Patients, and the Number of OM's in Their 1st Degree Relatives.

No. of cancers	No. of cases	Mean age	Std.Dev.	St.Error
0	394	47.99	11.59	0.58
1	115	50.89	9.87	.92
2	27	55.07	8.19	1.57
3	2	55	11.31	8.00
4	1	48		
Total	539	48.98	11.22	0.48

Table 3. Bilateral Involvement and FH of BC.

	Positive FH	Negative FH	Total
UnilateraL	146	356	512
Bilateral	9	7	16
Total	155	363	528

Table 4. Stages of the Patients and the Mean Age of their Cancer-afflicted Relatives.

Patients' stages	Mean rel.age	Std.Dev.	Std.Error
Stage I	61.03	14.96	2.88
Stage IIA	54.16	16.25	1.75
Stage IIB	54.09	15.14	1.84
Stage IIIA	49.87	16.15	2.58
Stage IIIB	46.51	16.54	4.98
Total	53.85	16.00	1.05

Although FH of BC or OM was not generally associated with tumour size, an FH of BC at or before age of 36 among 1st & 2nd degree relatives (n=15) was associated with larger tumour size (Mean tumour size 4.64 vs. 2.99 cm, t=2.381, df=490, sig.=0.018). Interestingly, FH of BC or OM was not associated with the duration of delay between patient's awareness of the warning sign, and visiting the doctor (Average of 7.53 and 8.86 weaks for patients with positive and negative FH of OM and 8.24 and 8 weaks for patients with and without FH of BC respectively).

Vascular invasion was noted more among patients with FH of BC, though the correlation was not significant (p=0.078)(Table 5). It was also associated with the more number of OM cases in the pedigrees in 3rd and 4th degree relatives (p=0.03). Again, mean age of the BC-afflicted relatives was less among patients who had detectable vascular invasion in their tumours (50.97 vs. 56.19 yrs., t=-2.04, df=151, p=0.043).

Moreover, lymphatic invasion was associated with FH of OM (chi-square=9.794, df=1, sig.=0.002) (Table 6). Mean number of OM cases per pedigree was 0.62 and 1.06 in patients whose tumours had and didn't have lymphatic invasion respectively (t=-2.392, df=313, sig.=0.017) and the correlation was more significant considering the 1st and 2nd degree relatives (p=0.008). Also mean number of all cancers (BC and OM) per pedigree was higher among patients whose tumours had significant lymphatic invasion (0.28 vs. 0.52 for 1st degree [t=-2.16, df=313, sig.=0.031] and .57 vs. 1

Table 5. Vascular Invasion and FH of BC.

	FH(+)	FH(-)	Total
With vascular invasion	53	99	162
Without vascualr invasion	40	116	156
Total	93	215	318

Table 6. Lymphatic Invasion and FH of OM.

	FH(+)	FH(-)	Total
With lymphatic invasion	19	35	54
Without lymphatic invasion	147	104	251
Total	166	139	305

for 2nd degree relatives[t=-2.73, df=313, sig.=0.007]).

ER and PR staining was not associated with FH of BC or OM at all. However, tumours of the patients who had FH of prostate or esophagous cancers were mostly ER positive (p=0.025 and p=0.02 respectivly), though the limited number of the cases restricts the validity of this finding.

Conclusions

Family history (FH) is the most important and perhaps one of the most controversial risk factors of breast cancer (BC). A positive FH of BC and OM is a frequent finding which could double the risk of BC occurance. Moreover, it is readily accessible and does not necessitate time and money consuming procedures. However, it takes patience, tact and attention to draw a detailed and percise pedigree and also, valid documents to confirm the diseased relatives among the families; otherwise, it might be quite possible to take an innocent mass for a malignant tumour. We believe that tight family bounds and close relationship in Iranian families could increase this validity.

Previous studies have showed that the tumour behaviour of the patients with a FH of BC is somehow different, with a trend towards a less aggressive state and better prognosis. The reason is not clear, but it has been attributed to the patients' increased awareness of the disease, which would lead to the earlier detection of the tumour.

However, we did not find any significant differences between the time period between patients' first detecting the tumour, and visiting the physician, for cases with and without FH of BC or OM. Also tumour size (which could be used as a rough estimate of the course of the disease) was not different among patients with and without FH of BC and/or OM in our study. These findings suggest the involvement of other causative factors.

Also the mere FH of BC was not associated with FH of OM, the number of OM's increased significantly with number of BC's in the pedigrees.

Cases with bilateral involvement mostly had FH of BC. It is quite expectable since the same factor(s) which had increased the incidence of BC among relatives could increase the chance of BC occurance in other breast of the patient.

We found that patients who had a history of BC at or before the age of 36 among their 1st and 2nd degree relatives, had also more aggressive tumours (i.e. bigger size and more vascular invasion). This finding confirms the importance of stratifying the BC afflicted relatives according to age together with emphasis on the degree of relatives in risk assessment.

But perhaps the most striking finding of this study was the impact of FH of other malignancies (OM) on patients' tumour behaviour. Cases with FH of OM were significantly older than the ones without it. According to the type of cancers, this effect was noted among patients with FH of prostate cancer and leukaemia and also uterus cancer among their 1st degree relatives. Also, FH of esophagous cancer (which is rather common in Iran) was associated with a lower stage and more ER staining. ER staining was also noted more among tumours of the patients with FH of prostate cancer. These findings support the less aggressive nature of these tumours.

On the other hand, FH of OM was associated with higher grade of the patients' tumour and also more lymphatic invasion. Considering the consensus that older age of onset is associated with better prognosis, the later finding seems to pose us with a paradox.

Once again, taking a look at the age of the cancer afflicted relatives was helpful; the younger the age of relatives diagnosed with cancer, the higher the stage of the probands themselves.

Prognostic value of FH of BC is perhaps not a new idea and other investigators have worked on it (though there still exists much work to do in this regard), but as our data show, FH of OM might be an other prognostic factor in BC patients, which could have complex effects on tumours' behaviour, regarding type of cancer and the age-degree of the afflicted relatives. Further study will clarify details of this association.

But what will be the next step? Cancer occurance is the result of a complicated interaction between the inherited (genetic) and aquired (enviromental) factors. Presence of a history of BC or OM in one's family could be indicative of the possibility that something is predisposing the family members to cancer and the propability increases with the number of detected cases. But here, our main enigma is that, "Are the factors which predispose the individuals to BC the same factors that determine the invasiveness of the occurred tumours?"

Our findings confirm that these two phenomena (i.e. initiation and progression) are at least to some extent distinct in BC and they function separately (sometimes even opposingly). FH of BC and/or OM increases the odd of BC occurance, but it is not essentially associated with a worse prognosis. This scope might help in building a model of progression from normal breast tissue toward benign and precancerous lesions and eventually a fully invasive malignant tumour, similar to the model which has been suggested for colorectal carcinomas.

The authors are fully aware of the limitations of their study. Relying on the patients' and their relatives' claims and shortage of firm evidence, weaken the validity of the pedigrees but we took advantage of reports whenever possible. Also, rather low frequency of some cancers, increases the occurance of accidental associations and decreases the reproduciblity of the findings.

The patients are being continuously followed up but the 6-year time period between the inclusion of the first and the last case has made it somehow difficult to assess the survival indices of the patients in the present article.

Genetic analysis is another factor which would be helpful in identifying the role of FH in BC. The patients and their selected relatives are being analyzed and screened for sporadic and familial mutations in namely BRCA1 and 2, p53 and APC genes in both tumour and blood speciments. Follow-up of the studied population and genetic analysis is being carried out and will be published subsequently.

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